Medical and Pediatric Oncology 29:190–196 (1997)

Multimodal Therapy for Children and Adolescents With Ewing Sarcoma: Results of the First National Chilean Trial (1986–1991)

Milena Villarroel, MD,[1]* Juan Tordecilla, MD,[2] Carmen Salgado, MD,[3] Xialong Luo, PhD,[4] Susana Messen, MD,[5] Yolanda Rayo, MD,[8] Paola Zolezzi, MD,[6] Jaime Rojas, MD[7]

Thirty-seven patients with Ewing sarcoma were treated in the First National Chilean Trial for Ewing's Sarcoma (1986–1991), which comprised the St. Jude Ewing's 78 Study. All patients received cyclophosphamide, doxorubicin, vincristine, and Dactinomycin for a total treatment period of about 10 months, and all prescribed therapy was administered. Local therapy consisted of irradiation (RT) to the primary tumor, complete surgical resection, or a combination of both surgery and RT. Twenty-nine of these patients had localized tumors, 24% had pelvic primary tumors, 21 were males, and 20 were greater than 10 years of age at diagnosis. Twenty-one patients had tumors that were greater than 8 cm in largest diameter. Fourteen of the 29 patients with localized disease remain disease free at 23 to 91 months from diagnosis. Fourteen patients have died of tumor-related complications and 1 of a secondary malignancy. Relapse was local only in 4, metastatic in 9, and local plus metastatic in 1. Only 1 of the 8 patients with metastatic disease at presentation remains disease free. Toxicity consisted primarily of myelosuppression and mucositis. We conclude that this form of relative intense multimodal therapy for children/adolescents with localized Ewing sarcoma is curative in about half of affected children as in the original St. Jude study, and that it can be safely given in a developing country, provided that careful attention to supportive care and treatment planning is given. Although these results represent improvement in outcome for our patients, more effective therapy is needed for children with Ewing sarcoma, especially those with metastatic disease at presentation. Med. Pediatr. Oncol. 29:190–196, 1997.

Key words: Ewing sarcoma; bone tumor

INTRODUCTION

Wider use of multimodal therapy, including radiation therapy (RT) and/or surgery and multiagent chemotherapy (doxorubicin and cyclophosphamide ± actinomycin-D ± vincristine), dramatically changed the cure rate for children and adolescents with Ewing sarcoma during the past quarter century, from about 15% in the 1960's to 50 to 60% presently [1]. Refinements in RT have improved local control [2], and surgery in place of, or in addition to, irradiation for expendable bones is increasingly being used in an effort to limit late effects of therapy and to improve local control and survival further [3]. Despite these notable advances, the global war against this and other forms of childhood cancer is being lost, since most children live in developing countries which lack access to the modern therapy required for cure. To address this problem in part, we introduced a national trial of relatively intense multimodal therapy in 1986, modeled after a pilot trial reported from St. Jude Children's Research Hospital [4]. Our aim was to cure more children/adolescents with Ewing's sarcoma in Chile.

Hayes et al. [4,5] first reported that sequential administration of cyclophosphamide and doxorubicin, based on cell kinetic principles, was both feasible and effective in the treatment of Ewing sarcoma in children and adolescents in 1983. Moderate dose intensity of both cyclophosphamide and doxorubicin was achieved without undue toxicity; the treatment was well tolerated, easy to administer, and given over a short period of time; and overall outcome was relatively good [5]. Further, isolated metastatic recurrences were rare, suggesting that such therapy was highly effective in eradication of micrometastases [4]. Based on the favorable results of this pilot study, the Programa Infantil Nacional de Drogas Antineoplásicas (PINDA) embarked on a similar study with

[1]Calvo Mackenna Children's Hospital, Santiago, Chile; [2]Hospital de Niños Dr. Roberto del Rio, Santiago, Chile (J.T.).; [3]Hospital de Niños Exequiel González Cortés, Santiago, Chile; [4]St. Jude Children's Research Hospital, Memphis, Tennessee; [5]Hospital San Juan de Dios, Santiago, Chile; [6]Hospital Regional Valdivia, Valdivia, Chile; [7]Hospital Guillermo Grant B. Concepción, Chile; [8]Hospital Van Buren, Valparaíso, Chile.

Programa Infantil Nacional de Drogas Antineoplásicas (PINDA) (Chilean cooperative group for treatment of pediatric cancer).

Supported in part by the National Cancer Institute (P30 CA-21765) and the American Lebanese Syrian Associated Charities (ALSAC).

*Correspondence to: Milena Villarroel, M.D., Hospital Calvo Mackenna, Antonio Varas 360, Santiago, Chile.

Received 2 August 1996; Accepted 16 December 1996

TABLE I. Characteristics of 37 Patients With Ewing Sarcoma

Patients, total	37
Follow-up	23–91 months (median, 60 months)
Sex	
Male	21
Female	16
Age	3–18 years (median, 11 years)
⩽10 years	17
>10 years	20
Time from symptoms to diagnosis	15 days–27 months (median, 3 months)

TABLE II. Primary Sites for 37 Patients With Ewing Sarcoma

Extremities	No. of patients	Axial	No. of patients (percent)
Humerus	5	Pelvis	9 (24)
Radius	1	Rib	3
Femur	4	Vertebrae	4
Tibia	2	Ethmoid	1
Fibula	1	Mandible	1
Foot	4	Scapula	1
Total	17		19
Extra osseus	1		

the aim of demonstrating feasibility of administration of this form of therapy in a multicenter study in a developing country. We also sought to evaluate the effectiveness of such therapy when applied to our patient population. Specifically, we wished to estimate the cure rate (i.e., 7-year relapse-free survival, RFS) in this setting and to gain experience with surgical resection as a means of achieving control of local disease. Gross estimates of the local control rate with chemotherapy and surgery, with or without irradiation, were to be compared with the control rate achieved with chemotherapy and standard local radiation therapy. Secondary aims were to identify prognostic factors and define the spectrum of toxicity for this type of therapy when given in our environment.

PATIENTS AND METHODS

Forty-four previously untreated patients with initial histological diagnoses of Ewing sarcoma entered the study between August 1986 and December 1991. Thirty-seven of these patients were eligible and evaluable and are therefore the focus of the remainder of this report. Reasons for inevaluability included noncompliance with protocol (2), incorrect diagnosis (1), and lost to follow-up (4). The median follow-up is 60 months (range, 23–91 months). Twenty-one patients were male (M:F = 8:5). The median age was 11 years (range, 3–18 years); 4 patients were less than 5 years old at diagnosis (Table I). Because of the small number of patients presenting with metastatic disease, we have chosen to focus this paper primarily on the 29 eligible patients who presented with localized tumors.

The time interval from symptoms to diagnosis ranged from 15 days to 27 months (median, 3 months, Table I). The interval was greater than 6 months for 12 patients. Five patients underwent one or more previous biopsies due to initial diagnoses of osteomyelitis.

The sites of primary tumor are shown in Table II. Nearly one-fourth had pelvic tumors. One patient had an extraosseus Ewing tumor. Twenty-nine patients had localized tumors; 8 (22%) had metastatic disease (lung, 4; bone, 2; lung and bone, 2). Sixteen patients (2 with metastatic disease) had primary tumors ⩽8 cm measured on a pre-therapy radiograph or computerized tomography (CT) scan, and 21 (6 with metastatic disease) had tumors >8 cm in the largest dimension.

Pre-treatment investigations included history, physical examination, complete blood count, bone marrow examination, renal and liver function tests, and echocardiogram. Postero-anterior and lateral radiographs of both the chest and primary bone lesions, and a bone scan with technetium-99 polyphosphate, were performed in all cases. A CT scan of the primary tumor and of the chest was also performed in 14 of these.

The histologic diagnosis of Ewing sarcoma was based on standard morphologic criteria applied to the examination of stained slides of representative tumor tissue sections obtained by open biopsy. In one case, electron microscopic evaluation was used to substantiate the histologic diagnosis. No cytogenetic studies were performed.

Systemic Therapy

Patients were treated on a protocol which was based upon the Ewing's '78 Protocol from St. Jude Children's Research Hospital (Table III) [5]. All patients received induction chemotherapy with 5 courses of cyclophosphamide, 150 mg/M^2/day for 7 days, and doxorubicin, 35 mg/M^2 on day 8, with courses beginning on days 1, 15, 29, 50, and 71.

Continuation chemotherapy consisted of weekly vincristine 1.5 mg/M^2 (maximum, 2 mg) for 11 weeks and dactinomycin 1.5 mg/M^2 (maximum, 2 mg) given every 2 weeks for 6 doses. This therapy was followed by 6 more courses of sequential cyclophosphamide and doxorubicin given at 3-week intervals. The total duration of therapy was approximately 10 months.

Local Therapies

Local therapies for the 29 evaluable patients with localized Ewing sarcoma were individualized with an emphasis on the use of surgery plus chemotherapy for local control. All patients received initial multiagent chemo-

TABLE III. Schema, Dosages, and Route of Administration of Therapy for Chilean Ewing Trial I (1986–1991)

Phase*	Dosage
Induction	
Cyclophosphamide	150 mg/M^2/day for 7 days × 5 courses beginning on days 1, 15, 29, 50 and 71
Doxorubicin	35 mg/M^2 on day 8 of each course beginning on days 1, 15, 29, 50 and 71
I	
Vincristine[a]	1.5 mg/M^2 weekly × 11
Dactinomycin[a]	1.5 mg/M^2 every 2 weeks × 6
II[b]	
Cyclophosphamide	150 mg/M^2 m/day × 7 days
Adriamycin	35 mg/M^2 on day 8

*Phase I was repeated after phase II in patients with metastatic disease only.
[a]Maximum per dose, 2 mg
[b]Every 21 days × 6 courses (of cyclophosphamide adriamycin)

TABLE IV. Localized Ewing Sarcoma: Patterns of Relapse and Treatment Outcome

Patients, total	29
No. (%) of patients/surviving disease-free	14 (48%) (23–91 months; median, 53 months)
Deaths	15 (6–62 months; median, 19 months)
Relapsed	14 (4–62 months; median, 9.5 months)
local recurrence	4 (14%)
metastatic disease	9 (29%)
local & metastatic	1
Second malignancy	1

therapy. Local therapy comprised radical surgery (i.e., amputation or limb salvage, 6), tumor resection (2), resection followed by radiotherapy (8), or RT alone (11). The remaining 2 patients with localized Ewing sarcoma did not complete local therapy because of early relapse before local therapy was attempted (1) or early progressive disease with multiple bony metastases (1).

Patients treated with RT plus chemotherapy received an RT dose ranging from 45 to 63 Gy (median, 50 Gy). Five of these patients had primary pelvic sites. Other sites included scapula (1), humerus (2), femur (2), and vertebra (1). In the 8 cases treated with surgery followed by RT, the radiation dose ranged from 30 to 50 Gy. For this group primary sites included humerus (3), vertebra (1), ethmoid bone (1), tibia (1), inguinal soft tissue (1), foot (1).

Of the 8 patients treated with surgery plus chemotherapy only, radical surgery (i.e., limb salvage or wide enbloc resection) was employed in cases of limb primary tumors or expendable bones (i.e., astragalus, calcaneus, and fibula). Only 2 patients underwent amputation. One patient was a 6-year-old who underwent amputation below the knee because of his young age (i.e., 6 years) and the expected morbidity of RT to this site; the second patient had an amputation because of initial misdiagnosis as osteosarcoma of the femur. Two patients had rib primaries and one a pelvic primary tumor which were completely resected.

Patients were reevaluated for response by diagnostic imaging studies, and then assigned a clinical response category using the following criteria: CR, complete resolution of all tumor (primary and metastatic sites), with improvement in bone lesions (i.e., evidence of decreasing tumor size and/or bone healing) by radiographs, bone scans, and, when available, CT, and absence of tumor cells on bone marrow examination; PR, >50% regression of tumor(s) at all sites; and NR, <50% regression of all tumor sites or progressive disease occurring during the period of induction therapy. The patients with tumors in dispensable bones or that were considered to have an indication for surgery (e.g., an expendable bone) underwent a surgical procedure with the intent to completely remove the tumor if possible and to histologically document their response status. When the tumor was completely excised with negative margins, patients received no RT to the primary tumor site. If there was an incomplete resection with gross residual tumor or microscopic residual disease, RT, 50 Gy or 30 to 35 Gy, respectively, was given. Irradiation was delivered to involved fields plus a margin of 3 cm limited to the residual soft tissue disease as seen in the post-induction evaluation.

This study was retrospective in nature. Relapse-free survival (RFS) curves were drawn after calculation by the method of Kaplan and Meier [6]. Comparisons between groups were made using the log-rank test [7]. Seven year relapse-free survival was used as an estimate of cure because hazard estimates appeared to be zero thereafter.

RESULTS

Patients With Localized Tumors at Diagnosis

Of 29 patients with localized Ewing sarcoma, 14 (48%) remain disease-free with a minimum of 2 years follow-up (Table IV and Fig. 1). Fourteen other patients have relapsed in local sites only (4 of 29, 14%), metastatic (9 of 29, 29%), or local plus metastatic sites (1) [5]. One additional patient developed a second malignancy. All 5 local recurrences were within the irradiated volume which included the primary tumor. The relapses occurred at times ranging from 4 months to 62 months from diagnosis (median, 9.5 months). Ten of the 14 patients who failed therapy (71%) developed metastases, with or without local recurrence, four others experienced only local relapse. The final patient who failed developed a paravertebral ganglioneuroma at 45 months and a suprarenal neuroblastoma 5 years from diagnosis. This case could have been misdiagnosed initially or may represent a second malignancy (Table IV). Thus the Kaplan Meier es-

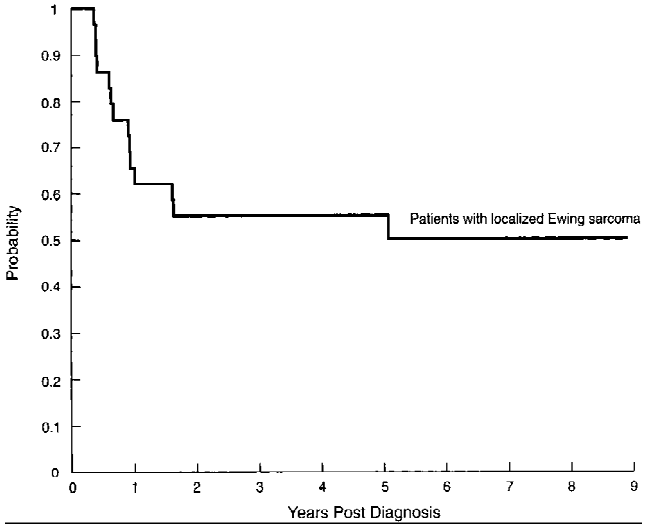

Fig. 1. Kaplan Meier estimates of relapse-free survival for 29 patients with localized Ewing sarcoma treated on the National Chilean protocol between 1986 and 1991.

timate of 7-year RFS for these patients is 50% ± 15% (Fig. 1) and of overall survival is 53% ± 14%.

Patterns of Recurrence in 29 Patients With Localized Ewing Sarcoma According to Local Treatment

Local therapy was individualized and consisted of radical surgery (i.e., amputation or limb salvage, 6), local wide resection of the tumor (2), resection followed by RT (8), or RT alone (11). Two patients were not evaluated for local treatment effect, and 1 patient, with a tumor of the radius, relapsed within the interval between completion of induction chemotherapy and surgery, after attaining partial remission.

Of 11 patients treated with irradiation to the primary site and chemotherapy, 7 experienced local (3) or distant relapse (4) at a median time of 12 months (range, 5–20 months). All of these cases had primary tumors >8 cm in diameter, and only 1 of these patients had attained a CR after induction therapy (Table V). All received irradiation at a dose of 45–50 Gy to the primary tumor.

Eight of the 29 patients with localized tumors were treated with surgery plus chemotherapy, without RT. Three of these 8 patients experienced metastatic relapse (bone, 3; lung, 1).

Eight cases were treated with RT, surgery and chemotherapy (30–50 Gy, median, 50 Gy). One of these patients developed bone metastases 5 years from diagnosis and a second patient developed a second malignancy 45 months from diagnosis.

Patients With Metastatic Disease at Diagnosis

Of 8 evaluable patients with metastatic disease at diagnosis, only 1 patient with a vertebral tumor and a skull metastasis is continuously disease-free for 56 months.

TABLE V. Tumor Recurrences, According to Radiation Dose, Tumor Response Assessed by Computerized Tomography Scanning, and Tumor Sites in Patients With Localized Primary Tumors Treated With Irradiation Only*

Site	CT Response	RT (Gy)	Relapse	Time (months)
Humerus	CR	50	Local	8
Humerus	Progression	50	Metastases	5
Femur	Progression	50	Metastases	20
Femur	PR	50	Local	12
Pelvis	PR	50	Metastases	12
Pelvis	PR	45	Local	12
Pelvis	PR	50	Metastases	12

CR = complete response; PR = partial response
*All of the tumors were >8 cm in diameter

His local treatment comprised RT, 50 Gy, and he received no irradiation to the metastatic site. The other 7 patients died with evidence of local and metastatic disease 1–27 months after diagnosis (median, 10 months).

Prognostic Factors

Analysis of 7-year DFS according to patient characteristics (Table VI) showed that patients with pelvic lesions fared worse than patients with tumors in other sites (29% ± 24% vs. 57% ± 15% $p = 0.05$). Patients with extremity tumors fared similarly to those with tumors in other sites (7-year DFS 48% ± 24% vs. 50% ± 16%, $P = 0.92$ respectively). Also, patients with tumors treated locally with surgery, or with surgery plus RT fared somewhat better than did patients treated by RT alone (50% ± 18% and 70% ± 22%, 36% ± 29%). However, this difference was not statistically significant, $P = 0.24$. Finally, patients who achieved complete responses to induction chemotherapy fared better than those who attained partial remissions (7-year DFS, 72% ± 17% versus 33% ± 19%, $p = 0.017$) (Table VI).

Acute Toxicity of Therapy

Patients received all scheduled chemotherapy. The significant toxicities observed are summarized in Table VII and included sepsis (5), vomiting (27), hemorrhagic cystitis (3), mucositis after dactinomycin, which occasionally resulted in up to 10% weight loss (25), peripheral neuropathy (4), and myelosuppression (ANC < 500/mm^3, $n = 37$). However, only 5 febrile episodes during periods of severe neutropenia required admission for intravenous antibiotics. Transient cyclophosphamide-associated hemorrhagic cystitis was associated with previous pelvic RT, 50 Gy, in 2 of 3 cases.

DISCUSSION

The results of this first national Chilean trial for children/adolescents with Ewing sarcoma indicate that it is

TABLE VI. Seven-Year Disease-Free Survival for Patients With Localized Ewing Sarcoma According to Tumor Site, Type of Local Therapy, and Degree of Local Response

Variable	7 years DFS	*P* values
Site of primary tumor		
Extremities versus other sites	48% ± 24% vs. 50% ± 16%	0.92
Pelvis versus other sites	29% ± 24 vs. 57% ± 15%	0.05
Size of primary tumor		
⩽8 cm	59% ± 17%	0.26
>8 cm	43% ± 23%	
Local treatment[a]		
Surgery	50% ± 18%	0.24
Surgery + RT	70% ± 22%	
RT	36% ± 29%	
Response to induction CT[a]		
Complete remission (15/29, 52%)	72% ± 17%	0.017
Partial remission (10) or progression (2) (12/29, 41%)	33% ± 19%	

[a]Two cases were inevaluable for response to induction therapy (1 developed local progression before local therapy was given, and 1 had significant delay in local therapy due to infection of a surgical wound that developed metastatic recurrence before local therapy).

TABLE VII. Types of Toxicity

Toxicity (Moderate/Severe only)	Number of Cases
Vomiting	27
Myelosuppression	37
Sepsis	5
Mucositis	25
Peripheral neuropathy	4
Hemorrhagic cystitis	3
Skin reaction	1
Phlebitis	1
Myocarditis	1

feasible to deliver multimodal therapy, as required for patients with Ewing sarcoma, in the multiple centers throughout Chile that comprise the PINDA. Further, effectiveness of the therapy employed for Chilean patients with localized Ewing sarcoma appears to be similar to that reported from the original St. Jude Ewing's '87 trial [4,5]. We attribute the success of this trial to the wide availability of cancer chemotherapeutic drugs made available through the Ministry of Health by the government of Chile at no cost to the PINDA or to patients, and to the willingness of Chilean pediatric cancer treatment specialists nationwide to support a national treatment protocol.

Cancer is the second most common cause of death from disease in non-neonate children less than 15 years of age in Chile [8] and thus it assumes considerable importance to the people of Chile. We have taken the approach of first organizing a national pediatric cancer treatment group to pool intellectual and patient resources, and then adopting highly successful protocols, developed and tested elsewhere, as a first step toward obtaining the experience and discipline necessary for excellence in care and clinical research. The results of this trial and others for different types of childhood cancer in Chile encourage us to believe that we too can reach the high level of success achieved with therapy in the United States and Western Europe during the past quarter century. We have demonstrated the feasibility of delivering this frequently curative therapy in our medical setting, its toxicity profile when given in this environment, and its relatively high level of effectiveness for our patients with localized Ewing sarcoma. This accomplishment has formed a benchmark of success in treatment to which we will compare future results of studies that will increasingly incorporate research questions asked to advance the field.

The demographic and clinical features of our patients are similar to those observed in other series [1,4,5,9–17]. Our results compare favorably with several studies initiated in the 1980s that now have long follow-up. For example, Bacci et al. [14] reported 5-year disease-free survival of 41% with a median follow-up of 9 years for 144 patients with localized Ewing sarcoma of bone. Long follow-up is important in establishing cure rates in Ewing's sarcoma since patients can experience late relapse. Our results are similar to those originally reported from St. Jude for patients with localized tumors (64% RFS at 3 years for the St. Jude study and 59% RFS at 3 years for our study). The relatively small difference in outcome could be due to the small number of subjects in both studies or to minor differences in the patient population. Also, it may be important that for most of this study we did not have CT scanning routinely available for staging or for treatment planning. Since CT is more sensitive than routine radiographs for imaging chest metastases [18], it is possible that we inadvertently classified some patients as having localized disease that with more accurate imaging would have been found to have metastatic disease at diagnosis. We also found a slightly lower rate of local relapses as compared to the original St. Jude study (17% vs. 25%) but a similar rate of metastatic recurrence. This observation could indicate less good documentation of local relapse in our study, since neither biopsies nor CT scanning of the primary lesion was routinely performed at the time of relapse.

Similar to findings of other studies, we, too, found that patients with localized smaller tumors fared somewhat better than did patients with larger lesions at the time of diagnosis, although the difference in our study was not significant. Also, those with complete tumor response early fared better than did other patients [19,21,22]. Our small study size precludes an extensive search for prognostic factors.

We acknowledge that lack of central review of pathology material, port films for RT planning, and details of

surgical therapy represent suboptimal documentation of the quality of our data. However, economic considerations precluded inclusion of these quality control measures in this study. We hope to implement central review in future studies.

Our patients treated with surgery for primary tumor control appeared to fare better than those treated with RT alone (50% vs. 36% at 7 years). However, such patients typically had smaller tumors, and therefore may well have fared better than other patients regardless of the type of therapy used for local control. In this regard, it should be emphasized that patients who failed to respond to RT had larger tumors and responded less well to induction chemotherapy, indicating that they were prognostically unfavorable at diagnosis.

Children who develop metastatic disease during or after treatment and those with metastatic disease at the time of presentation pose especially difficult treatment problems [1,10,12,23]. Metastatic recurrences were a problem in this study in that they comprised about two-thirds of failures, even in the group of children who initially had localized disease; all patients who developed this complication ultimately died of their disease.

Results of treatment for children with metastatic Ewing's sarcoma at diagnosis have remained poor for more than 25 years, although some improvement in outcome has occurred over this time period (i.e., zero in the 1960s to about 30% presently) [23]. Only 1 of our 8 patients with metastases at diagnosis remained relapse-free for 5 years. This especially poor result may be due to our small sample size, failure to include CT positive only patients in the group due to lack of availability of CT imaging of the chest for most patients, or inadequate effectiveness of the therapy used. We are addressing this problem in our present study by intensifying multiagent chemotherapy and adding the drug pair etoposide and ifosfamide. This drug pair has been shown to be highly active in patients who have relapsed on therapy that included cyclophosphamide [24], and it improved survival in the subset of newly diagnosed patients with nonmetastatic Ewing sarcoma in one large, randomized study [25]. Thus we anticipate substantial improvement in both the degree and frequency of tumor regression using this more intensive chemotherapy, which should expand opportunities for subsequent surgical extirpation of the primary tumor. We expect that survival will improve as well.

We are confident that better definition of tumor volume for planning RT field size, with use of routine CT scanning, will help improve local control and potentially RFS [18]. We are planning to use twice daily hyperfractionation of RT in an effort to diminish late effects and improve local control even further, especially in patients who cannot have their tumors completely resected because of size and location (e.g., large pelvic primaries). We are confident that these significant changes can be delivered nationwide in Chile. Further, it is likely that more intense therapy will improve outcome further [18], since such therapy has already been shown to favorably impact RFS for patients with localized disease in several large studies conducted in the United States and Europe [25,26]. In future studies we look forward to introducing research questions into our protocols, most likely by collaboration with other countries in order to accrue sufficient patients to answer randomized questions.

ACKNOWLEDGMENTS

We gratefully acknowledge Drs. William M. Crist and Gaston K. Rivera (St. Jude Children's Research Hospital, Memphis, TN) for helpful advice in the preparation of this manuscript.

REFERENCES

1. Horowitz M, DeLaney T, Malawer M, Tsokos M: Ewing's sarcoma family of tumors: Ewing's sarcoma of bone and soft tissue and the peripheral primitive neuroectodermal tumors. In Pizzo PA, Poplack DG (eds): ''Principles and Practice of Pediatric Oncology.'' Philadelphia: Lippincott, 1993, pp. 795–821.
2. Razek A, Perez CA, Tefft M: Intergroup Ewing's sarcoma study: Local control related to radiation dose, volume, and site of primary lesion in Ewing's sarcoma. Cancer 46:516–521, 1980.
3. Neff JR: Nonmetastatic Ewing's sarcoma of bone: the role of surgical therapy. Clin Orthop 111–118, 1986.
4. Hayes FA, Thompson EI, Meyer WH, Kun L, Parham D, Rao B, Kumar M, Hancock M, Parvey L, Nagill L, Hutso HO: Therapy for localized Ewing's sarcoma of bone. J Clin Oncol 7:208–213, 1989.
5. Hayes FA, Thompson EI, Hustu HO, Kumar M, Coburn T, Webber B: The response of Ewing's sarcoma to sequential cyclophosphamide and adriamycin induction therapy. J Clin Oncol 1:45–51, 1983.
6. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457–481, 1958.
7. Peto R, Pike MC, Armitage P: Design and analysis of randomized clinical trials requiring prolonged observation of each patient. II. Analysis and examples. Br J Cancer 35:1, 1977.
8. Instituto Nacional de Estadística. Ministerio de Salud Servicio de Registro Civil e Identificación. Anonymous annuario de demografía national 1993. Republica de Chile. 1995 (Yearly book of demographic features).
9. Tepper J, Glaubiger D, Lichter A, Wackenhut J, Glatstein E: Local control of Ewing's sarcoma of bone with radiotherapy and combination chemotherapy. Cancer 46:1969–1973, 1980.
10. Philips RE, Higginbotham NL: The curability of Ewing's endothelioma of bone in children. Pediatr 70:391–397, 1967.
11. Nesbit ME, Gehan EA, Burgert EO, Vietti TJ, Cangir A, Tefft M, Evans R, Thomas P, Askin FB, Kissane JM, Pritchard DJ, Herrmann J, Neff J, Makley J, Gigula L: Multimodal therapy for the management of primary, nonmetastatic Ewing's sarcoma of bone: A long-term follow-up of the first Intergroup study. J Clin Oncol 8:1664–1674, 1990.
12. Rosen G, Caparros B, Nirenberg A, Marcove R, Huivos AG, Kosloff C, Lane J, Murphy L: Ewing's sarcoma: Ten-year experience with adjuvant chemotherapy. Cancer 47:2204–2213, 1981.
13. Wilkins RM, Pritchard DJ, Burgert, Jr., Unni KK: Ewing's sar-

coma of bone. Experience with 140 patients. Cancer 58:2551–2555, 1986.
14. Bacci G, Toni A, Avella M, Nantrini M, Sudanese A, Ciaroni D, Boriani S, Emiliani E, Campanacci M: Long-term results in 144 localized Ewing's sarcoma patients treated with combined therapy. Cancer 63:1477–1486, 1989.
15. Jurgens H, Exner U, Gadner H: Multidisciplinary treatment of primary Ewing's sarcoma of bone. A 6-year experience of a European Cooperative Trial. Cancer 61:23–32, 1988.
16. Zucker JM, Henry-Amar M, Sarrazin D, Blanche R, Patte C, Schweisguth O: Intensive systemic chemotherapy in localized Ewing's sarcoma in childhood. A historical trial. Cancer 52:415–423, 1983.
17. Bacci G, Picci P, Gherlinzoni F: Localized Ewing's sarcoma of bone: Ten years' experience at the Istituto Ortopedico Rizzoli in 124 cases treated with multimodal therapy. Eur J Cancer Clin Oncol 21:163–173, 1985.
18. Parker BR, Moore SG: Imaging studies in the diagnosis of pediatric malignancies. In Pizzo PA, Poplack DG (eds): ''Principles and Practice of Pediatric Oncology.'' Philadelphia: Lippincott, 1993, pp. 152–178.
19. Oberlin O, Patte C, Demeocq F: The response to initial chemotherapy as a prognostic factor in localized Ewing's sarcoma. Eur J Cancer Clin Oncol 21:463–467, 1985.
20. Evans R, Nesbit M, Askin F: Local recurrence, rate and sites of metastases, and time to relapse as a function of treatment regimen, size of primary, and surgical history in 62 patients presenting with non-metastatic Ewing's sarcoma of the pelvic bones. Int J Radiat Oncol Biol Phys 11:129–136, 1985.
21. Gobel V, Jurgens H, Etspuler G: Prognostic significance of tumor volume in localized Ewing's sarcoma of bone in children and adolescents. J Cancer Res Clin Oncol 113:187–191.
22. Hayes FA, Thompson EI, Parvey L, Rao B, Kun L, Parham D, Hustu HO: Metastatic Ewing's sarcoma: Remission induction and survival. J Clin Oncol 5:1199–1204, 1987.
23. Meyer WH, Kun L, Marina N, Robertson P, Parham D, Rao B, Fletcher B, Pratt CB: Ifosfamide plus etoposide in newly diagnosed Ewing's sarcoma of bone. J Clin Oncol 10:1737–1742, 1992.
24. Grier H, Krailo M, Link M: Improved outcome in nonmetastatic ewing's sarcoma and PNET of bone with the addition of ifosfamide and etoposide to vincristine, adriamycin, cyclophosphamide, and actinomycin: A Children's Cancer Group and Pediatric Oncology Group report. Proc Amer Soc Clin Oncol 13: 421(Abstract), 1994.
25. Barbieri E, Emiliani E, Zini G: Combined therapy of localized Ewing's sarcoma of bone: Analysis of results in 100 patients. Int J Radiat Oncol Biol Phys 19:1165–1170, 1990.